

Genetic Variation of Fatty Acid Oxidation and Obesity, A Literature Review

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ABSTRACT

Modulation of fat metabolism is an important component of the etiology of obesity as well as individual response to weight loss program. The influence of lipolysis process had receives many attentions in recent decades. Compared to that, fatty acid oxidation which occurred after lipolysis seems to be less exposed. There are limited publications on how fatty acid oxidation influences predisposition to obesity, especially the importance of genetic variations of fatty acid oxidation proteins on development of obesity. The aim of this review is to provide recent knowledge on how polymorphism of genes related fatty acid oxidation is obtained. Studies in human as well as animal model showed that disturbance of genes related fatty acid oxidation process gave impact on body weight and risks to obesity. Several polymorphisms on CD36, CPT, ACS and FABP had been shown to be related to obesity either by regulating enzymatic activity or directly influence fatty acid oxidation process. (*Int J Biomed Sci* 2016; 12 (1): 1-8)

Keywords: obesity; genetic; fatty acid; lipolysis; metabolism

INTRODUCTION

In this modern era, the awareness of obesity as important health risk is increasing. From several investigations on mechanism of obesity, systemic lipid metabolism appeared to be a hot topic. Studies done using different approaches rose a same agreement that disturbance in fat metabolism is not only a risk for developing of obesity but

also an important factor that influence successfulness of weight loss program in obese individual. Previously, it was found that lipolysis in obese and overweight individual is impaired (1). Genetic studies showed that polymorphism of genes related lipolysis influenced weight loss in obese subjects during weight loss although results are still controversial (2-8). Furthermore, Rogge (9) proposed that fatty acid oxidation (FAO) is also an important factor that influences development of obesity in human. In the review, the author stated that the individual differences of FAO not only give contribution for development of obesity but also complicate weight loss treatment.

Recent studies demonstrated that the differences between healthy lean individual and obese in the term of energy metabolism included 4 factors: reduction of FAO, increasing demand of glucose for ATP synthesis, lower basal ATP concentration and accumulation of lipid in muscles and several other organs (9). Reduction of FAO was discovered to be related to nutritional status. Studies in hu-

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man showed that pre-obese subjects and formerly obese subjects have lower fat oxidation than lean counterpart as shown by increasing respiratory quotients (RQ). Filozof *et al.* (10) compared 8 obese individuals who had lost BMI from more than 30 kg/m² into 24.5 ± 1.0 kg/m² with 8 never-obese individuals (24.4 ± 1.0 kg/m²). Under the same weight maintenance diet (50% carbohydrate, 30% fat and 20% protein) for 3 days, post-obese subjects had higher RQ showing less FAO compared to never-obese subjects with the comparable body weight.

RQ describe how much energy that is used from carbohydrate and this is important for weight maintenance. In a population-based study, Seidell *et al.* (11) showed that increasing RQ as well as reduction of FAO were related to weight gain. This lower FAO was found increasing dependency of glucose as the source of energy. One of the important factors that contribute to lower FAO in obese individuals has been investigated before. Simoneau *et al.* (12) studied changes in enzymatic activity of FAO at muscle tissue in obese and lean individuals. They showed that FAO related enzymes such as CPT (carnitine palmitoyl transferase) and CS (citrate synthase) (will be discussed later) were lower in obese subjects compared to lean subjects. Interestingly, they also reported that weight reduction by a very low calorie diet and behavioral changes did not affect the level of those enzymatic markers (12).

It has been suspected that changes in CPT activity had a big influence on the weight regulation due to its importance in regulating ATP production from fat. Ragge argued that reduction of CPT reduce uptake of fatty acid by mitochondria, promotes lipogenesis and therefore reduce energy supply for physical activity (9). This reduction of CPT then contributes to higher body weight and individual ability to regain weight after weight loss. This theory had a significant influence to support the findings that obese individuals are resistance to lose weight. As reported by many studies, reduction of body weight was followed by reduction of energy expenditure, thus gave the unwanted effect of given weight treatment. Study done by Elia *et al.* (13) proved that obese people had different response to starvation than their normal counterpart. In the starving condition obese subjects used less fatty acid and ketone bodies for ATP production than lean subjects while protein loss and oxidation in obese subjects were higher than normal subjects.

Ragge proposed an interesting theory on the interaction between obesity and low oxidation status. In the review, it was stated that sedentary characteristics of sedentary lifestyle from obese individual not only the cause of

obesity. Instead, obese people tend to be more sedentary in order to achieve more favorable energy balance. As mitochondria have less ability to convert energy from fatty acid, and produce more lactate, obese individuals are more likely to experience fatigue. On the other hand, high AMP:ATP ratio as the result of lower oxidative capability also induce neuroendocrine signals thus make those people are continuously seeking energy-dense food (9).

DISCUSSION

The Fatty Acid Oxidation Pathway

Mitochondria are important place where fatty acid can be oxidized because it contains all enzymes that is necessary for FAO. FAO is started with transportation of fatty acid into mitochondria, followed by carnitine shuttle and ended with β -oxidation cycle. This fatty acid is taken from circulation after hydrolysis of triglyceride and lipoprotein by lipoprotein lipase (LPL) in endothelium (14). In cytosol, fatty acid should be transported into mitochondria and the length of carbon atom of each fatty acid defines how this molecule transported. Both long chain fatty acid (LCFA) and very long chain fatty acid (VLCFA) require transporters to enter mitochondria. Kiens (15) reviewed that at least three protein that involved in this transport system, those are: fatty acid transport protein (FATP), plasma membrane-bound fatty acid binding protein (FABPpm), and fatty acid translocase (FAT/CD36). FATP is a transmembrane protein which important not only to transport fatty acid but also to convert VLFA and LCFA into Acyl-CoA (14). Recent reports demonstrated that expression and activity of these LCFA/VLCFA transporter enzymes were changed due to certain conditions including diet, exercise and obesity. Long term high fat diet was successfully increase level FABPm protein in muscle tissue while carbohydrate rich diet reduce the level (16). Obese individuals had higher FABPm protein expression compared to lean subjects¹² and this increment also found in male subjects in the exercise group (17).

In order to get into inner side of mitochondria, acyl-CoA that is produced by FATP should be converted into another form using carnitine shuttle system. This system is basically formation and deformation of acylcarnitine by the help of three important proteins CPT1 (carnitine palmytoyltransferase 1), CACT (Carnitine acylcarnitine translocase) and CPT2 (carnitine palmytoyltransferase 2). CPT1 converts Acyl-CoA into acylcarnitine at the outer membrane of mitochondria. Acylcarnitine thus transported through inner membrane of mitochondria by CACT

and then converted again into acyl-coA by CPT2 (14). The importance of carnitine shift on entering fatty acid into mitochondria makes proteins in this system become important in the regulation of β -oxidation. Once Acyl-CoA inside mitochondria, oxidation initiated by acyl-coenzyme A dehydrogenase (ACAD) (14).

Components of Fatty Acid Oxidation

ACS. Acyl-CoA synthetase (ACS) is an important enzyme that provides substrate for both lipogenesis and oxidative process. This metabolite is not functionally limited to fatty acid metabolism but also can alter many important processes including insulin secretion and glucose transport (18, 19). In its protein structure, ACS has a region for AMP binding site and a region for fatty acid binding site (20). ACS has several isoforms and is located differently. ACS1 is located in the intrinsic membrane of endoplasmic reticulum (ER) and mitochondrial-associated membrane (MAM), ACS4 is located in the MAM fraction and ACS5 is located in the outer membrane of mitochondria. It was suggested that the different location of ACS isoforms also influences its function in an independent pathway (18, 20). From those isoforms, ACS1 is suggested to be related to oxidation since its expression is increased by induction of Peroxisome Proliferator Activated Receptor α (PPAR- α) (21, 22).

CD36. CD36 is a lipid transport protein which is involved in many cellular processes including FAO. This protein is expressed in several tissues such as adipose tissue, intestine and vascular endothelial (23). CD36 is composed of intracytoplasmic domains and an extracellular domain. The hydrophobic region is located in the extracellular domain which suggests an interaction with the plasma membrane (24). Deficiency of CD36 had an influence on fatty acid metabolism which is proven by a lower rate of plasma fatty acid clearance after a meal (25).

FABP. Fatty acid binding protein is an important protein which targets fatty acids into the FAO pathway. In general, this protein has a high affinity for LCFA, both saturated and unsaturated. FABP is expressed almost in every tissue (26). Although the main function of FABP is diverse in different tissues, its function in each tissue varies accordingly. In adipose tissue, FABP influences TG storage, inflammation as well as regulates fatty acid species in plasma (26). Expression of FABP in skeletal muscle is related to FAO and esterification of LCFA (27, 28). In the liver, FABP also brings its ligands to the FAO pathway as well as interacts with transcription factors such as PPAR α (26, 29, 30).

FATP. Together with FABP and CD36, FATP helps fatty acids find their way to the oxidation pathway. Additionally,

this protein also helps LCFA transferred into mitochondria by adding acyl-coA on the fatty acid carbon chain. This additional acyl-coA activates LCFA so CPT1 can use that as a substrate. This protein is membrane bound and expressed in skeletal muscle and adipose tissue (31-33). Located in mitochondria, the expression of FATP affects FAO. FATP1 is one of the six FATP isoforms that is present in skeletal muscle which contains an AMP-binding motif for transport function (34).

CPT system. Carnitine Palmitoyltransferase (CPT) system is composed of two important proteins, CPT1 and CPT2. CPT1 is located in the outer membrane of mitochondria while CPT2 is located inside mitochondria. CPT1 processes acyl-CoA made by FATP into acylcarnitine by incorporating a carnitine molecule. This acylcarnitine can enter the layer of mitochondria thus CPT2 converts that back into Acyl-CoA (35). Although located and functionally different in oxidation pathways, both proteins share similarity (CPT1-A and CPT2 share 50% of homology) (36). There are three isoforms of CPT1: CPT1-A (expressed in liver, kidney, lung and spleen); CPT1-B (expressed in skeletal muscle, heart, adipose tissue and testis); and CPT1-C (expressed in brain) (35).

Control of Fatty Acid Oxidation

Schreurs *et al.* (37) previously described three ways in regulating β -oxidation through enzymes such as ACS and CPT1 as well as metabolites like malonyl-coA. Principally, FAO is regulated by the early flow of the CPT1 system (38, 39). Malonyl-CoA is a potent inhibitor of CPT1 which is catalyzed by ACC (Acyl-CoA Carboxylase) (38). The other regulator of FAO is hormones. There are evidences showing that insulin and thyroid hormones were able to regulate the sensitivity of CPT1A but not CPT1B to malonyl-CoA in the liver (40, 41). It seems that differences in the regulation of CPT1A and CPT1B are tissue specific. For instance, in muscle tissue CPT1B is regulated by PPAR α and retinoid X receptor.

ACC is an enzyme that is involved in the regulation of FAO in the human body as well as the regulation of lipogenic processes. This enzyme is important because it produces malonyl-CoA, a potent CPT inhibitor. Thus, the activity of this enzyme is an important communication process between lipogenic signals and FAO signals (37). The regulation of ACC is done via AMPK and protein kinases that control this phosphorylation also control ACC activity (42). Furthermore, transcription factors that are related to cholesterol and carbohydrate metabolism are also known to regulate ACC. Sterol regulatory element binding protein (SREBP1c) was

reported to modify ACC expression as the response to diet or hormonal signals (43-45). There is also a study showing that carbohydrate responsive element binding protein (ChREBP) is involved in regulation of ACC (46).

FAO can also be altered by environmental trigger such as diet and exercise. In the case of obesity, this becomes more important because it will define the successfulness of weight loss intervention. A review done by Kiens *et al.* (47) nicely discussed an environmental factors that influences FAO in human. Dietary pattern influence the availability of important nutrients in the body. The state of carbohydrate storage, is able to affect FAO in human body. Roepstorff *et al.* (48) reported that higher glycogen storage will lead to lower FAO. On the other hand, Helge *et al.* (49) investigated the effect of prolonged fat-rich diet on FAO. In the study, they found that fat rich diet increased fat-oxidative capacity after 7 weeks. There are some interesting points on how diet-exercise correlates with FAO. It has been reported that FAO is lower when an individual receive carbohydrate rich diet 3-5 days before exercise compared to those with fat-rich diet. Thus it was assumed that diet had important effect on the preference of energy source during exercise, rather than exercise itself (50-52).

Considering exercise is an important factor to control FAO, it is necessary to keep in mind that there is no guarantee increasing intensity will always accompanied by increasing of FAO. As demonstrated by Romijn *et al.* (53), total FA oxidation reach its highest point at 65% of maximal oxygen uptake. This data is taken based on comparison between 25%, 65% and 85% of maximal oxygen uptake during training. Several theories have been proposed to answer how exercise influences oxidation in human body. Firstly, the increment of capillary density is observed due to endurance training. There also report on how this training increased lipid binding proteins and some enzymes involved in FAO (15). The enzymes related lipolysis such as ATGL and HSL were also increased after training suggesting that capacity of skeletal muscle tissue to use stored fat as energy were increased (54).

The impact of exercise on FAO pathway and the regulation on oxidation process has already investigated before. In early 80's, Holloszy and Coyle (55) reported that endurance training increased mitochondrial contents of skeletal muscle thus improve its ability to use fat as the source of energy. Following reports argued that quality of skeletal muscle also determines the ability of muscle tissue to better oxidize fatty acid. In an *in vitro* study, Sahlin *et al.* (56) showed that the proportion of type I fibres influenced FAO. The molecular control of FAO during exercise is still

under investigation. However, several investigations have been made to clarify the role of proteins related oxidation on control of FAO. It was shown that expression of FAT/CD36 influenced FAO in mitochondria. An interesting report showing that mitochondrial density of CD36 is higher in slow-twitch muscle, type of muscle that had higher maximal capacity of FAO. This protein also increased about 63% after 120 min of aerobic exercise explaining the importance of this protein for balancing energy source during exercise (56-60).

Genetic Polymorphism of Fatty Acid Oxidation Related Proteins and Weight Loss

Skeletal muscle is an important component of the body that regulates energy expenditure not only because of its ability to use glucose and fatty acids as the source of energy, but also because this tissue is 40-50% of total body mass in adults (61). There are several proteins that expressed in skeletal muscle cells and influence its ability to "burn" more fat into energy. Thus genetic variations of proteins in FAO pathway were reported to be related to several traits including obesity. Some investigations revealed that polymorphism of genes in this pathway were also related to ability of obese/overweight individuals to weight loss during lifestyle intervention.

ACSL. There are six ACSL (long chain acetyl-coA synthase) family members identified in human and their polymorphisms were reported to influence ACS ability to initiate FAO. Variation on rs2419621 has been shown to influence weight loss in obese individual (62). This finding was also accompanied by the fact that T allele in this region increased ACSL transcription level in muscle (62). Teng *et al.* (61) investigated the role this polymorphism on expression level of ACSL using electrophoretic mobility shift assay (EMSA). They demonstrated that T allele was able to form an E-box element upstream of the second ACSL5 isoform transcript start site while C allele of this variant lacked of the third E-box element. This formation of E-box element is related to increment in ACSL5 promoter activity, thus lack of this element reduced the activity (61).

Interestingly, several other genes have been reported to produce proteins with Acyl-coA synthetase activity including SAH, MACS1, MACS2 and MACS3 (63). Although it is not clear whether those genes are directly involved in the regulation of FAO in human skeletal muscle, the polymorphism of this genes were reported to influence on weight status. Genetic polymorphism of SAH influenced body mass index, lipid profile and waist hip ratio (63). The

other studies found that the interaction between SAH and obesity is obesity related (65, 66). This finding was also confirmed by the other study showed that MACS2 polymorphism was also influence those phenotypes (64). Until today, there is not many data on the underlying mechanism of how this polymorphism is related to obesity or weight loss. And because this protein is involved in two contradicting processes, oxidation and lipogenesis, it is not simple to take a conclusion which parts that plays role the most in ACSL polymorphism.

CD36. Recently Love-Gregory and Abumrad (25) discussed the influence of CD36 gene polymorphism and obesity as well as obesity related complications. In the review, they stated that genetic variations of CD36 were not strongly associated with obesity. Polymorphism of CD36 gene was more likely to be associated with metabolic disorder such as abnormal FFA, HDL and LDL levels (67-69). One potential explanation of how the expression of this gene influenced metabolic profile had been investigated by Kennedy *et al* (70). Adipose tissue of CD36^{-/-} mice was more insulin sensitive and had lower inflammation compared to wild type model shown lack of CD36 were metabolically protective.

There is a controversy on how genetic variations in CD36 influence obesity. A study done in European adolescent population showed that four SNPs in CD36 (rs3211867, rs3211883, rs3211908 and rs1527483) was related to obesity, BMI and percentage of body fat (71). This finding was inconsistent with study done by Choquet *et al*. (72) who found no significant correlation between those variations on obesity. This meta-analysis done from 3 European countries (German, French and Finland) showed no effect on this polymorphism on obesity. Interestingly, they also discovered that polymorphism of rs3211883 was associated with obesity but with opposite direction from that found by Bokor *et al* (71, 72).

An investigation done in Europe showed a promising result on how CD36 influence individual susceptibility to obesity. Corpeleijn *et al*. (73) provides an important finding that -178A>C polymorphism of CD36 had influence on fasting fat oxidation of 722 obese subjects from 7 countries including The Netherlands, Denmark, France, Spain, United Kingdom, Czech Republic, and Sweden. The relationship is still significant even after adjustment with fat mass, HOMA index and free fatty acid level. In contrast, a case control study on 30 obese and 30 non obese children tried to link between CD36 polymorphism and glucose metabolism. However this study showed no relationship between CD36 variants and glucose metabolism. This

study also failed to show the effect of CD36 polymorphism and plasma level of CD36 (74). Perhaps this is due to the expression of this gene is that mainly on skeletal muscle or gastrointestinal tracks but not in circulation.

FABP. To elucidate the influence of liver FABP (L-FABP) on obesity and weight gain, recent investigation by Atshaves *et al*. (75) used L-FABP ablated mice model. In their study they observed that mice with loss of L-FABP gain more fat tissue mass as well as weight than the wild type. Additionally, mice with L-FABP ablation also reduced their fat oxidation. The authors argued that L-FABP KO mice with high-fat diet due to lack of fatty acid transport to liver, LCFA is allocated more on storage rather than oxidation. Another study using adipose FABP (A-FABP) and intestinal (I-FABP) also find the similar result that mice lack of this gene increased body weight compared to wild type mice (76, 77).

There is limited publication on how genetic variation in this gene influence body weight or obesity and several studies failed to prove this association. Hayakawa *et al*. (78) investigated the impact of alanine to threonine substitution at codon 54 of the fatty acid binding protein 2 (FABP2) gene on obesity and insulin resistance in 258 Japanese subjects. However, the result showed no correlation between this polymorphism and obesity as well as other metabolic abnormalities. In African American individuals, Lei *et al*. (79) also found no difference on the risk of obesity between subjects with FABP 2 Thr54 alleles but they had small increasing of BMI compared to subjects without Thr54 alleles.

Ala54Thr variant allele of FABP2 gene might influence metabolic rate of individual thus gives an impact on obesity risk. This hypothesis was tested by Takakura *et al*. (80), a group of scientists from Japan, who investigated the influence of genetic variations of FABP2 on Japanese obese women. In this study, 80 obese women participated in a lifestyle intervention including diet and exercise. Interestingly, subjects with Thr variant had lower resting metabolic rate and waist circumference after diet and physical exercise therapy and those without Thr variant. Subjects with Thr allele also reported higher body weight at age of 20 than subjects without Thr. Despite of lack of repetition and evidence support, examining the role of FABP in the response of weight loss therapy would be interesting in the future.

CPT. Robitaille *et al*. (81) investigated the role of CPT1 gene on obesity though a diet-gene interaction. They sequenced CPT1 gene from French-Canadian population and found 14 genetic variation in CPT1A and 26 varia-

tions in CPT1B. From those variations CPT1B c.282-18C > T and p.E531K variants were related to obesity. Furthermore, CPT1A A275/A275 variant on high fat diet had higher BMI compared to those on low-fat diet. This confirmed that those variant is more affected by high-fat diet since subjects with T275 allele shown no influence of fat intake on obesity parameters.

A recent report done in Alaska Native Health Research showed the relationship between genetic variants of CPT1A and obesity traits. About 28 SNPs of CPT1A were analyzed from these 1141 Yup'ik Eskimo. From those SNPs, P479L SNP was shown to be related to several parameters of obesity including BMI, percentage of body fat, waist and thigh circumference. Subjects with L479 allele had lower percentage of those obesity traits than those with P479 allele. Lemas *et al.* (82) also shown several SNPs that also involved in obesity phenotypes, such as thigh circumference (rs2278908, rs2278907, P479L, rs4930248, rs11228372, rs11228373, and rs3019594), hip circumference (rs2278907, rs11228372, rs11228373 and rs3019594). This study confirmed previous clinical investigation of L479 allele of P479L variant in CPT1A gene done by Brown *et al.* (83). In an observation of six L-CPTI deficient patients they demonstrated that L479 allele diminished CPT1A enzyme activity in fibroblast cells as well as the ability of malonyl-coA to inhibit CPT1A.

CONCLUSION AND FUTURE REMARKS

It was evident that fatty acid oxidation is an important process that influence the ability of body to reduce fat by diet and physical activity. Changes in this process were also linked to occurrence of obesity and several metabolic diseases. Studies in human as well as animal model showed that disturbance of genes related fatty acid oxidation process gave impact on body weight and risks to obesity. Several polymorphisms on CD36, CPT, ACS and FABP had been shown to be related to obesity either by regulating enzymatic activity or directly influence fatty acid oxidation process. However, those studies are lack of repetition and in some cases the findings were controversial. Further studies are necessary to clarify potent SNPs on those genes and the interaction with environmental factors including diet and physical activity, two processes that is tightly involved in fatty acid oxidation process. It will also be interesting to study the effect of high fat isocaloric diet on individual with certain genetic variations on FAO pathway to cross validate the diet-gene interaction in weight loss program.

CONFLICT OF INTEREST

The author declare that there is no conflict of interest in the making of this manuscript.

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